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*THE PHYSIOLOGY OF INTERNAL SECRETIONS.**

WE owe the term 'internal secretions' to Brown-Séquard,† by whom it was first used in published communications dating from 1891. The essential idea conveyed by the expression, however, is not new, as it has been stated more or less clearly by many previous writers in their speculations upon the probable functions of the so-called ductless or vascular glands. It had long been recognized that these glands possess no excretory ducts, and that, therefore, whatever secretion they may produce probably enters the blood either directly or by way of the lymph. Haller* is credited with stating this view with regard to the thyroid as early as 1776, and according to Pettit† a similar view was advanced by Schmidt in 1785 with regard to the suprarenals. Toward the middle of the present century this belief was generally accepted for such glands as the thyroid, suprarenals, thymus, hypophysis cerebri and spleen, but as early as 1869 Brown-Séquard seems to have suggested the view that all glands, whether possessed of excretory ducts or not, give off something to the blood that is of importance in the general nutrition of the organism. From 1889 his ideas took definite shape in numerous publications‡ upon the physiological effects of injections of extracts of the testis. At first he did not use the term internal secre-

*Paper read at the 4th Triennial Session of the Congress of American Physicians and Surgeons.

† Brown-Séquard and d'Arsonval: Comptes rendus de la Société de Biologie, 1891.

* Jones in Todd's Cyclopædia of Anatomy and Physiology: Article on Thyroid Gland.

† Pettit: Recherches sur les capsules surrén ales, 1896—Paris. Thèse de la Faculté des Sciences.

‡ Brown-Séquard: Archives de Physiologie normale et pathologique 1889–92.

tion, and seems to have held the view, so far as the testis is concerned, that the material furnished to the blood is absorbed from the external secretion and is normally carried off in part in this secretion.

During this same period the brilliant results of the experiments made upon the thyroid glands and the pancreas were forcing themselves upon the attention of physiologists, and these results, together with his own experiments upon the extracts of testis and ovary, and his previously expressed belief as to the possible effect exercised by all glands upon the composition of the blood, seem to have led Brown-Séquard to the generalization expressed in the happy term 'internal secretion.' The term as used by him was not restricted to the glandular tissues alone, but was meant to signify that all the tissues in the body furnish something of special importance to the blood—that, in fact, every act of nutrition is accompanied by an internal secretion This broadening of the term to apply to all the tissues is logical, perhaps, but it must be admitted, I think, that so far as our actual knowledge goes it is not justifiable. The evidence derived from experimental investigations and clinical observations indicate that many, although not all, of the glandular tissues of the body as a result of their normal metabolism add something to the blood or affect its composition in some way, and that this activity is either essential or helpful to the maintenance of the normal functions of the organism. In this list we can place such glands as the liver, pancreas, thyroid and parathyroid bodies, suprarenal bodies, hypophysis cerebri, and probably the ovary, testis, thymus and spleen. But I know of no observations that force us to entertain a similar belief with regard to the non-glandular tissues, such as muscle, nerve and connective tissue.

So far as I am aware, there is no authorized definition of the term internal secretion, but, if we adhere closely to the facts in the case, the expression may be interpreted to mean certain products that are elaborated by gland cells from material furnished by the blood, which are afterwards passed back to the blood or lymph stream to subserve some function in general or special nutrition. From the standpoint of mechanism of secretion a useful distinction has been drawn between these internal secretions and secretions of the usual kind, or external secretions. The latter are in all typical cases poured out upon a free epithelial surface that communicates with the exterior, while the internal secretions are discharged upon the close endothelial surfaces of the blood and lymph vessels.

The definition given by Brown-Séquard, as we have seen, attributed internal secretions to all tissues. As a part of this general conception he was led also to restate what appears to have been a dream of the older physicians, namely, the view that all animal tissues might and ought to be employed in special cases as means of medical treatment, extracts of each organ or tissue being recommended for the particular disease supposed to be due to disturbance of function in the corresponding tissue. This general conclusion seems to have been a wide induction upon the basis of the incomplete facts known at that time with regard to the therapeutical use of extracts of thyroid and testis. It was not entirely justified by actual experience then or now, but the attractive possibilities it presents have doubtless been the cause of much of the general interest manifested in the subject of internal secretions. A new field, hitherto almost unexplored and full of promise for the discovery of medical specifics, seemed to be opened to the medical profession, and much activity has been exhibited in exploiting the possibilities of this kind of therapeutical treatment for

which the names *opotherapeutics*, *organotherapeutics* and *histotherapeutics* have already been suggested.

It must be borne in mind, however, that these promises are in large part premature. The one clearly successful method of treatment by animal tissues is the use of thyroid extracts, and the demonstration of the value of this method was the result of rigorous scientific work extending over more than a decade, and was obtained quite independently of the generalization announced by Brown-Séquard. It seems perfectly certain that whatever else of value may come out of the therapeutical application of tissue extracts must also be established by intelligent scientific research, on the side of experimental as well as clinical medicine, and not by indiscriminate and over-anxious attempts to secure immediate results.

It is my purpose to-day to call your attention briefly to some of the important results obtained by experimental physiology that tend to prove the existence of internal secretions in a number of glandular organs. The main interest to the physiologist lies, perhaps, in the light this work has thrown upon the functions of the blood-glands, or ductless glands, especially the thyroid, suprarenals, hypophysis cerebri, thymus and spleen. Forty years ago the physiology of these bodies was not only unknown, but was beyond the reach of intelligent hypotheses. Within recent years facts have accumulated, especially with regard to the thyroid and suprarenals, that give us a new standpoint from which to view their physiology—a standpoint also from which experimental investigations may be planned with reasonable hope of abundant success in the future. I shall not attempt an historical review of recent work in this subject, as this has been given already in numerous general addresses and special papers.* I desire only to emphasize what seems to be the outcome of the physiological work that has been done in the last twelve or thirteen years, and to explain briefly the character of the work now in progress.

If we include under the term 'thyroid tissue' not only the thyroid body itself, but also the accessory thyroids and the neighboring parathyroids, it has been shown beyond reasonable doubt that complete removal of this tissue in man and the related mammals is followed, as a rule, by serious disturbances of nutrition that are immediately or ultimately fatal to the animal. Moreover, in these cases the reintroduction of thyroid material into the body, whether this introduction be made by grafting the tissue, by subcutaneous or intravascular injections or by absorption from the alimentary canal, results in an amelioration or even entire removal of the symptoms of malnutrition. The physiologists recall with pleasure that these two fundamental facts were first discovered as the result of experimental work in physiology. The effects of complete thyroidectomy were first described by Schiff* in 1856, and the therapeutical use of thyroid tissue arose naturally from the grafting experiments of Schiff† in 1884 and the subsequent experiments of Vassale ‡ and of Gley § upon injections of thyroid extracts. The brilliant results that have followed the use of thyroid tissue in man in cases of myxoedœma, goitre, etc., are, too well known now to require more than a passing reference.

*See especially Abelous: *Revue générale des Sciences*, May 15, 1893.

Schäfer: Address in Physiology; Annual Meeting of the British Med. Assoc., London, 1895.

Meltzer: On Thyroid Therapy; *New York Med. Jour.*, May 25, 1895.

* Schiff: Untersuchungen über die Zuckerbildung in der Leber, etc., Würzburg, 1859.

† Schiff: Revue médicale de la Suisse romande, 1884.

‡ Vassale: Rivista sperimentale di freniatria, etc., Vol. XVI.; also Centralblatt f. d. Med. Wiss., 1891.

§ Gley: Comptes rendus de la Soc. de Biol., 1891.

It follows as a logical conclusion from the successful effects attending its therapeutical use, as well as from the evil effects of its destruction or removal, that the thyroid tissue produces, normally, something that is in some way essential to the nutrition of the body. What that something is has been revealed partially by the beautiful chemical and clinical researches of Baumann and Roos. Baumann * has succeeded in isolating a substance, thyro-iodin, or iodothyrin, as it has been named more recently, which, according to the experiments of Roos,† preserves the beneficial effects of thyroid tissue.

The chemical characteristics of this compound will doubtless be presented in Professor Chittenden's paper. It has proved to be a very stable compound, unaffected by boiling, by strong acids and by gastric digestion, and this fact may be taken as a complete disproof of a former view to the effect that the action exerted upon the body by thyroid tissue is due to the presence of special enzymes or ferments. The fact that extracts of thyroid tissue or iodothyrin when absorbed into the blood ameliorate or remove the evil effects resulting from loss of function of the thyroid, seems to prove at once that the normal function of thyroid tissues is not merely to excrete poisonous material from the blood after the manner of the kidneys. It indicates, on the contrary, that these tissues act normally by giving off a material to the blood that in some way affects favorably the nutrition of all or a part of the tissues of the body. In other words, the thyroid tissues form a true internal secretion. Histological research indicates that, so far as the thyroid bodies proper are concerned, this secretion is contained in the so-called colloidal material that accumulates in the interior of the vesicles, and that the mechanism of secretion consists in a rupture of the walls of the vesicles at some point whereby the contents are discharged into the surrounding lymph spaces.*

The most important fact that remains to be discovered is the manner of action of this secretion upon the tissues of the body. At present we can only speculate upon the answer to this problem. More experimental work is required before a definite solution can be reached. To account for the action of the thyroid secretion two main hypotheses have been proposed. According to one hypothesis the function of the secretion is antitoxic. In some way it antagonizes an unknown toxic substance supposed to be formed in the body in the course of normal metabolism. When the thyroid tissues are removed this poisonous material, being imperfectly excreted, accumulates in the blood and produces the fatal symptoms of thyroidectomy by a process of auto-intoxication. The other hypothesis assumes that the secretion of the thyroid acts normally by promoting or regulating the metabolism of other parts of the body, particularly, perhaps, of the nervous tissues. We might designate this as the trophic or neuro-trophic hypothesis. It is less specific than the antitoxic hypothesis, and therefore, perhaps, less objectionable in the present incomplete state of our knowledge; but as no decisive, or even probable, proof can be given for either view, it seems unnecessary to criticise the various facts brought forward in support of one or the other of them. The two great facts to be explained are: first, that complete removal of the thyroid tissues brings on a condition of malnutrition that seems to affect especially the central nervous system; and, second, that injection or ingestion of thyroid ex-

* Baumann: Zeitschrift für physiolog. Chemie, Bd. XXI., 1896; also Bd. XXII.

† Roos: Ibid Bd. XXII.

*Biondi: Berliner klinische Wochenschrift, 1888. Langendorff: Archiv für Physiologie, 1889, Suppl. Bd. Schmid: Archiv für mik. Anatomie, 1896.

tracts while the animal is in this condition restores its metabolism more or less completely to the normal state. While both of these facts are explicable in terms of either of the hypotheses mentioned, the trophic theory does not involve the somewhat strained assumption of an unknown toxic product of metabolism that can not be got rid of completely by the usual methods of excretion.

A very interesting phase of thyroid physiology that has recently come to the front is the nature of the functional relationship between parathyroid tissue and thyroid tissue proper, such as is found in the thyroid body and the accessory thyroids. The parathyroids seem to occur in all mammalia. According to a recent description by Kohn* there is always one of these bodies on each side attached to the external or posterior surface of the lateral lobes of the thyroid, while in some animals, *e. g.*, the dog, cat and rabbit, there is an additional one on each side, imbedded in the substance of the thyroid lobes. Histologically the structure of these small bodies bears no resemblance to that of the thyroid. They possess the general appearance of embryological tissue, and have, therefore, been regarded usually as an immature form of thyroid tissue, which, under the stimulus of increased functional activity, is capable of developing into normal thyroid structure. Satisfactory evidence is lacking that such a transformation does actually take place under the conditions supposed, as, for example, after complete excision of the two thyroid lobes. On the contrary, the evidence from histology, as well as from embryology, seems to indicate that the two tissues are not only fundamentally different in structure, but possibly are also different in origin.

On the physiological side Gley† was the first to prove the great importance of the parathyroids. He showed that in rabbits complete extirpation of the thyroid lobes alone is not followed by a fatal result so long as the parathyroids remain. Removal of both thyroids and parathyroids, however, is in most cases followed by typical symptoms of complete thyroidectomy ending in the death of the animal. This latter result has been contested by some observers, but renewed investigations have demonstrated its accuracy. Gley explained his results on the hypothesis that after removal of the thyroid its function is vicariously assumed by the parathyroids. He concluded, therefore, that the functional value of the two tissues is identical. Recent work, however, tends to throw doubt upon this conclusion. Vassale and Generali* state that in dogs and cats removal of all four parathyroids produces the acute symptoms of complete thyroidectomy, and finally causes the death of the animal, in spite of the fact that the thyroid body proper is left practically uninjured. On the other hand, complete removal of the thyroid lobes is not immediately injurious to the animal, provided the parathyroids—or, in some cases, if even only one of the parathyroids—are left. They contend, therefore, that the result in dogs and cats usually attributed to extirpation of the thyroids is due in reality to the simultaneous removal of the parathyroids.

This result is partly confirmed by the independent experiments of Rouxeau† and of Gley.‡ The former finds that in rabbits complete removal of the thyroids alone causes no trouble, at least no immediate trouble, while excision of the external parathyroids alone is followed frequently by death, or by convulsive symptoms. Gley

*Kohn: Archiv für mik. Anatomie, Bd. 44, 1894.

†Gley: Archives de Physiologie normale et pathologique, 1892.

*Vassale and Generali: Archives italiennes de Biologie, XXV. and XXVI., 1896.

†Rouxeau: Comptes rendus de la Soc. de Biologie, Jan. 9, 1897.

‡Gley: Ibid.

reports some incomplete experiments upon rabbits and dogs that tend in the same direction. Finally, Moussu,* from experiments made upon mammals and birds, attempts to define in general terms the difference in function between thyroid and parathyroid tissue. According to his experiments, removal of the parathyroids alone is followed by certain acute troubles, such as have been usually described as the result of complete thyroidectomy, while removal of the thyroid lobes alone is followed by chronic troubles of nutrition which he designates as myxoedœmatous or atrophic cretinism. This last result has not been confirmed, so far as I am aware, by others, so that it cannot be accepted with entire confidence. It will be noted, however, that the tendency of this recent work is to show that the functional value of the thyroids and parathyroids is not identical, and that the importance hitherto attributed to the thyroids must be assigned, in part at least, to the parathyroids. The very great interest that these results may have when applied to human pathology and therapeutics will be evident to everyone.

Finally, a word may be said as to the possibility that other tissues exist in the body capable of replacing entirely or in part the functions normally performed by the thyroids or the parathyroids. This possibility seems to be indicated by the fact, commented on by most experimenters in in this field, that occasionally animals are found in which apparently complete removal of all the thyroid tissue, including the parathyroids, is not followed by a fatal result. Such cases may be explained by assuming the existence of accessory thyroids or parathyroids that escape the attention of the operator, but it is also possible that they may be due to the fact that there are other organs in the body that possess a thyroid function. Experiments in this direction have been made upon the spleen and the hypophysis cerebri. With regard to the former organ the results may be considered as entirely negative, while as regards the hypophysis the evidence is unsatisfactory. Some details concerning this last organ will be presented later.

The results of recent physiological experiments upon the suprarenal bodies have not been less interesting, although less complete than those upon the thyroid. These curious bodies, like the thyroid, are found constantly in all classes of the vertebrates, and seem, therefore, to be organs of fundamental importance. As long ago as 1856 Brown-Séquard* stated that extirpation of both suprarenals is usually fatal to the animal, death occurring generally very shortly after the operation, more rapidly, according to this observer, than after removal of both kidneys. This statement has been questioned frequently by other observers, but the results of the renewed investigations that have followed upon the recent revival of interest in the physiology of the ductless glands seem to corroborate fully the account given by Brown-Séquard. In the case of dogs, according to Szymonowicz,† death follows the operation within fifteen hours. It has been shown, also, that in some species of animals accessory suprarenals are not uncommon, and it is possible that this fact may explain the survival of a certain number of animals after supposed complete extirpation of the suprarenals. Removal of only one suprarenal does not appear to cause any noticeable trouble. In the case of complete removal, followed by a fatal result, the prominent symptoms preceding death are extreme muscular weakness, asthenia, and, in the case of dogs examined

* Moussu : Ibid, Jan. 16, 1897.

*Brown-Séquard : Comptes rendus de l'Ac. des Sciences, XLIII., 1856. *Journal de la Physiologie*, I., 1858.

†Szymonowicz : Archiv f. d. gesammte Physiologie, LXIV., 1896.

during this period, a great fall in blood pressure, together with a feeble heart-beat. It will be noted that in cases of Addison's disease in man the important symptoms, in addition to the pigmentation, are also an asthenic condition of the muscles and the heart. What explanation have we to offer for the surprisingly profound effect produced upon the body by the removal of these small organs?

Unquestionably, the most significant facts with regard to this problem have been obtained from a study of the effects of injections of suprarenal extracts into living animals. A number of the earlier experiments of this kind, especially those performed upon rabbits, resulted in the death of the animal, the preceding symptoms being convulsive movements, followed by some paralysis. The really valuable results, however, have been obtained by a more exact study of the effects of such injections upon the vascular and respiratory organs. Most of our knowledge upon these points has been derived from the researches of Oliver and Schäfer,* and Cybulski and Szymonowicz.† These two sets of investigators published their results nearly simultaneously. The important facts determined by them, and since corroborated in many laboratories, are as follows: Extracts of the medulla of the suprarenal bodies injected into the veins of a living animal cause a pronounced slowing of the heart-beat and a large rise of blood pressure. If the animal is first given atropin to paralyze the inhibitory nerves to the heart, or if the vagi are previously cut, the injection causes usually a marked quickening, instead of a slowing of the heart-beat, and a greater, indeed often an extraordinary, rise of blood pressure. The respiratory organs are not affected so seriously, a temporary slowing and shallowing of the respiratory movements being the result usually noticed. The effect upon the heart and blood vessels is quite temporary. Its exact duration depends somewhat upon the dose, and in part upon other less evident conditions, but, as a rule, within a very few minutes the rise in blood pressure, as well as the slowing of the heart-beat, passes off completely. New injections will bring out promptly a return of the effect described, although a continued repetition of the injections at too close intervals results in a progressive diminution of their action. Tying off the kidneys does not appear to prolong the effects of an injection, so that we may conclude that the temporary character of the result produced is not caused by a rapid elimination of the active substance through the kidneys, although, according to Szymonowicz, a part of it, at least, is got rid of by this means. The rapid disappearance, however, of the effects of a maximal or supramaximal dose indicates that the active substance is either quickly destroyed in the tissues or is neutralized in some unknown way.

The physiological explanation of the slowing of the heart caused by the suprarenal extracts offers no difficulties. Since this effect disappears completely upon section of the vagi, or after the injection of a few milligrams of atropin, it can only be due to a stimulating action upon the central endings of the inhibitory fibres, that is, upon the so-called cardio-inhibitory center in the medulla. According to Oliver and Schäfer the inhibitory effect is felt mainly upon the auricles. The beats of this part of the heart become weaker and slower and may cease altogether, while the ventricular beats, although slower, are more vigorous. After the vagi have been cut, suprarenal extracts cause a quicker and, according to Oliver and Schäfer, who measured the extent of

*Oliver and Schäfer: *Journal of Physiology*, XVIII., 1895.

†Cybulski and Szymonowicz: *Gazeta Lekarska*, 1895. (Abstracted in Jahresb. d. Thier-Chimie, 1895. Also Szymonowicz: Archiv. für d. gesammte Physiologie, LXIV., 1896.

the contractions directly, a stronger beat. This accelerating effect upon the heart after removal of the inhibitory fibres is not due, as we might at first suppose, to a stimulation of the central ends of the accelerator fibres, since it is still obtained after section of the cord in the neck, or after extirpation of the first thoracic ganglia. It must, therefore, be due to a peripheral action of the extracts upon the heart itself, either upon the muscle of the heart directly (Oliver and Schäfer) or upon the so-called motor ganglia (Szymonowicz, Gottlieb).

The effect of the injections upon blood pressure has been explained differently by those engaged in the work. Both Oliver and Schäfer, and Cybulski and Szymonowicz, believe that the enormous rise in blood pressure is due mainly to a great constriction of the arterioles. According to the latter this constriction is brought about by a stimulating action of the extracts upon the vaso-motor centers in the medulla and cord, while according to Oliver and Schäfer the action is exerted directly on the muscles of the blood vessels. Szymonowicz admits that if the cord is cut just below the medulla a great rise of pressure can still be obtained, but he explains this by supposing that the extract acts on the spinal centers. He asserts that if the entire cord is destroyed a rise of pressure can no longer be obtained. The experiment that he gives to illustrate this last point is, however, far from being convincing. The protocol of the experiment shows that the act of destroying the cord in itself reduced the blood pressure to zero. Moreover Biedl* reports that he has been able to get a rise in pressure from injection of the extracts after complete extirpation of the cord. The evidence, therefore, seems to favor the view proposed by Oliver and Schäfer, and this view is still further supported by the fact that when the volume of a limb is measured plethysmographically it often shows a distinct diminution after suprarenal injection, even though its nervous connections with the central nervous system are entirely severed.

There are, however, some facts reported in the experiments made by different observers which indicate that the assumed action of the substance on the peripheral arteries does not alone account for all the changes produced in blood pressure. It is probable that the greater force of the heart-beat plays an important part, as Gottlieb* contends, in causing the increase of arterial tension. Thus Szymonowicz reports measurements of the pressure in the external jugular vein made during one of his experiments. According to this report the venous pressure rose and fell with the arterial pressure, which is not what one would expect to occur in the case of a general constriction affecting the arterioles alone. According to Bayliss and Hill,† also, the general venous pressure increases with the rise in arterial pressure. So in a number of the published tracings given by Oliver and Schäffer it appears that the vaso-constriction was more pronounced in the abdominal viscera than in the limbs, since the volume of the latter measured plethysmographically showed an increase of a passive character, apparently, while the volume of the kidney or spleen was greatly diminished.

The significance of the marked reaction exhibited by suprarenal extracts depends very largely upon the possibility of proving that the substance producing the reaction is formed normally within the gland. It is conceivable, of course, that in the dead gland post-mortem changes might cause the formation of a substance giving this reaction, although under the normal condi-

*Biedl: Wien. klin. Wochenschrift, IX., 1896.

* Gottlieb: Archiv f. exper. Pathologie u. Pharmakologie, XXXVIII., 1897.

† Bayliss and Hill: *Journal of Physiolology*, XVIII. p 352, 1895.

tions of life it might not exist. Fortunately, we have direct proof that the active substance in question is a normal product of the metabolism in the gland. Cybulski and Szymonowicz found that blood drawn from the suprarenal vein, when injected into the circulation of a normal animal, gives the same effect, although less in amount, as extracts of the suprarenal glands, while blood from other veins has no such action. This result has been denied by Oliver and Schäfer, apparently upon insufficient experimental grounds. Langlois,* on the contrary, has been able to corroborate this effect of suprarenal blood, and, in the laboratory at Baltimore, Dr. Dreyer has obtained clear proof of a similar action. It appears from Dreyer's experiments that the effect is not obtained in every animal, but in some cases the results are very positive, and in a matter of this kind the positive evidence is the most important. When we remember that we are dealing most probably with a material formed by the secretory activity of gland cells, and that the amount of this material may vary at different times or under different circumstances, it is not surprising that negative as well as positive results are obtained.

Since it seems certain that the substance does occur under normal conditions in the venous blood flowing from the gland, we are justified in concluding that it is a normal product of the metabolism of the medullary cells of the gland, and that it is discharged or secreted directly into the blood. It must, therefore, exert continually a stimulating effect upon the heart and blood vessels. In corroboration of this last conclusion we have some striking experiments recorded by Szymonowicz which show that after complete extirpation of the two glands the blood pressure becomes greatly depressed. Both Oliver and Schäfer, and Cybulski and Szymonowicz, conclude that the normal function of the suprarenals consists in furnishing this stimulating substance to the blood. The former observers believe that its effect is mainly upon the muscular tissue; that it has a general tonic or augmenting action on all varieties of muscle found in the body—the striated muscle as well as the cardiac and plain muscle tissue. Cybulski and Szymonowicz hold essentially the same general view, except that they believe that the substance acts upon the nerve centers controlling the muscular tissues rather than on these tissues directly. It is, perhaps, impossible at present to decide as to this detail. Oliver and Schäfer have shown, without much doubt, that the substance acts upon the blood vessels after their connections with the central nervous system have been completely severed, and, on the other hand, there is clear proof that it affects at least one part of the central nervous system, namely, the cardio-inhibitory center. Further experimenting will probably soon furnish more definite information upon the extent to which the muscular and the nervous tissues are affected by this substance. Upon either of the views proposed we can understand at once why removal of the suprarenals brings on a condition of muscular asthenia, and why the continual activity of these organs is so essential to the body as a whole. It is significant, in this connection, to recall that Oliver and Schäfer found that extracts of the suprarenals in cases of Addison's disease did not contain this stimulating substance. The hypothesis that the suprarenals secrete a stimulating substance that augments the tone of the muscular system, either directly or indirectly, is not the only one offered to explain the physiology of these bodies. According to some observers the main function of the suprarenals, like that of the thyroids, is to produce an anti-

* Langlois: Archives de Physiologie normale et pathologique, 152, 1897.

toxic secretion capable of neutralizing or destroying certain poisonous products of body metabolism. The toxic products in this case have been supposed to originate in the functional metabolism of muscular tissue, and the asthenic condition following upon extirpation of the suprarenals has been compared with the similar effect produced by injecting the extracts of fatigued muscles into the circulation. The main argument of those who hold to this view seems to rest upon the fact that the blood of an animal that has been deprived of its suprarenals and is beginning to show the typical effects has a toxic effect when injected into the circulation of another animal from which the suprarenals have been removed shortly before. The fatal symptoms are brought on by the injection more rapidly than would happen otherwise. One cannot feel a great deal of confidence in this argument as contrasted with the apparently direct evidence offered in favor of the stimulation hypothesis.

Unfortunately, the physiological evidence with regard to the importance of the suprarenals to the body has not found so satisfactory an application in practical medicine as in the case of the thyroids. Suprarenal extracts and tissue have been used in cases of Addison's disease, but the beneficial effects obtained have not been so clear as in the case of thyroid extracts. Some of the results reported, however, indicate that the method is at least a hopeful one in certain cases.

A third interesting member of the group of ductless glands is the hypophysis cerebri, and a few words may be said as to its supposed physiological activity. This gland is commonly described as consisting of two parts, the anterior and the posterior lobe. The histology and the embryology of the two parts indicate that they are entirely different in origin and in structure. The anterior lobe is evidently a glandular structure. It develops originally as a saccular invagination from the buccal epithelium, and has essentially the same origin in all the vertebrates that have been examined. According to Haller* it is not strictly a ductless gland, since it possesses an imperfectly developed system of ducts that opens between the dura and the pia mater. It is evidently a secreting structure, and the fact that its secretion is discharged between the meningeal membranes suggests some special connection with the physiology of the brain. Histologically its structure recalls that of the thyroid gland, particularly in the fact that a colloidal material is said to occur frequently in the lumina of the gland tubules. In some animals, *e. g.*, the dog and the cat, it is a very small body, but in others, as the rabbit, sheep, ox and man, it is of considerable size and bears every indication in its structure of being an active secretory organ.

The posterior lobe, on the contrary, is very small in all animals and has the appearance of being a rudimentary organ. It develops as an outgrowth from the infundibulum of the brain and is more properly spoken of as the infundibular lobe. Its histology is very incompletely known. According to Berkley† it contains numerous typical nerve-cells, ependymal cells and neuroglia, a number of glandular epithelial cells arranged in part to form tubes or closed vesicles that contain a colloidal material, and some curious structures resembling nerve and organs.

The observations bearing upon the functions of the hypophysis have been limited to the glandular lobe. On the pathological side it has been shown that in many, if not in most, of the cases of acromegalia the glandular lobe exhibits pathological changes. For this reason extracts of the gland have been

* Morphologisches Jahrbuch, XXV., 1896.

† Berkley: The Johns Hopkins Hospital Reports, IV., 1895.

used therapeutically in cases of acromegalia, and, according to some reports, benefits have followed the treatment to the extent that some of the disagreeable features have shown amelioration. The evidence from this side, however, is not satisfactory, and the nature of the connection between acromegalia and disturbance of the function of hypophysis, if any exists, needs more complete investigation.

The experiments made by the physiologists are also meagre and inconclusive. Gley* reports a set of experiments made upon rabbits, in which he attempted to destroy the gland by an operation from above. The experiments were made upon rabbits from which the thyroid lobes had been removed previously, with the idea of demonstrating that a similarity in function exists between the thyroid and hypophysis. All but one of the animals died, owing to the severity of the operation. In the single survivor it was noted that the animal exhibited at times spasmodic muscular contractions and some degree of paresis, and that it died about a year after the operation. On the assumption that the animal would have lived if the thyroid lobes alone had been removed, Gley concluded that the removal of the hypophysis had prevented the parathyroids from replacing completely the loss of the thyroid, and that, therefore, the hypophysis is related in function to the thyroid tissue. Naturally but little importance can be attached to a single experiment of this kind, and, so far as I know, the author has not repeated the investigation. Vassale and Sacchi† claim to have removed the hypophysis partially or completely in a number of animals by an operation through the base of the skull. In cases of complete removal the animal died within a short time—fourteen days or less—after exhibiting a number of symptoms similar to those caused by thyroidectomy, such as muscular tremors and spasms and the development of a cachectic condition. Most physiologists, I fancy, will accept these experiments also with some hesitation until they have been confirmed by other observers. The very severe character of the operation necessary to reach the gland makes it questionable whether the results reported were due to its removal alone, although the experiments were evidently made with great care.

Szymonowicz and also Oliver and Schäfer report experiments upon the effects of injections of extracts of hypophysis into the circulation of normal animals. Szymonowicz states that in two experiments he obtained a slight fall pressure and a quickening of the heart-beat. He concludes, therefore, that the physiological action of these extracts is opposed to that caused by extracts of the suprarenals. Oliver and Schäfer, on the contrary, report that extracts of hypophysis exert an effect very similar in some ways to that shown by suprarenal extracts. For instance, they cause a marked rise of blood pressure, together with an augmentation of the heart-beat. Unlike the suprarenal extracts, however, they do not produce a slowing of the heart-rate when the vagi are intact. Upon the basis of these incomplete experiments they draw the somewhat hasty conclusion that the hypophysis and the thyroid are not similar in function, and that the hypophysis is not capable of assuming vicariously the activities of the thyroid.

I have recently made a number of experiments upon this organ, the results of which have been quite uniform and in many respects very different from those obtained by the authors just quoted. My experiments were made with the hypophysis of sheep mainly, although at first the gland of the dog was also used. The extracts were

*Gley: Archives de Physiologie normale et pathologique, 1892, 311.

†Vassale and Sacchi: Archives ital. de Biologie, XXII., CXXXIII., 1895; also XVIII., 1893.

made in normal saline, or in glycerine followed by dilution with normal saline, and usually the fresh gland was employed. The experiments differed from those reported by others, in that extracts were made separately of the glandular and the infundibular lobe, and the physiological effects of each were tested by injection into the circulation of normal dogs. It was found that the extracts of the glandular lobe have little or no perceptible effect when injected alone. Extracts of the small infundibular lobe, on the contrary, have a distinct and remarkable effect upon the heart-rate and blood pressure, an effect which resembles in some respects and differs in others from that shown by suprarenal extracts.

Briefly stated, these extracts injected into the normal animal with its vagi intact cause a very pronounced slowing of the heart-beat, similar to that caused by suprarenal extracts, but lasting a much longer time. The heart-beat is not only slowed, but is considerably augmented in force, as is shown by tracings taken with a Hürthle manometer. At the same time the blood pressure rises to a considerable extent, owing, apparently, to a peripheral constriction of the blood vessels, since oncometric tracings from the kidney show that this organ shrinks greatly in volume. Usually the constriction of the blood vessels occurs first, so that the pressure rises for about 20 mms. or more more of mercury. This is succeeded sometimes by a temporary fall of pressure during which the heart-rate may be increased, and then the slowing of the heart begins, while the pressure rises again to a greater or less extent above the normal. This last effect continues for a relatively long time and passes off gradually. The slowing of the heart may continue for half an hour or longer. If the dose used is a maximal one, and a second injection is given too quickly afterward, little or no effect is obtained. If, however, the dose is not too strong, and sufficient time is given given for its action to wear of, a repetition of the effects is obtained, and this may occur a number of times, although the effects decrease progressively in intensity.

The effects of the injection are somewhat different if the vagi are previously cut, or if a little atropin is given to paralyze the inhibitory fibres. Under these circumstances the slowing of the heart-rate is very much less marked, although not entirely lacking. In round numbers it may be said that with the vagi intact the heart-rate is reduced about 50 per cent., while in the atropinized animal the reduction is about 20 per cent. It might be added that an animal deeply under ether alone behaves in this respect like an animal with its vagi cut. This result indicates that the slowing of the heart-rate in the normal animal is due in part, but only in part, to a direct action on the medullary centers of the inhibitory fibres. On the other hand, the rise of blood pressure after section of the vagi is greater. Usually the blood pressure rises rapidly for about 20 mms. of mercury; this is succeeded in some cases by a temporary fall, and then the pressure again rises rapidly, reaching a height, in some cases, nearly equal to that caused by suprarenal extracts. During this last phase the heart-beats are slower and more powerful, the effect in this respect differing from that caused by suprarenal extracts. The effect lasts longer than with suprarenal extracts, and a longer interval must be allowed before a new injection will give the same result. I have obtained a marked rise of pressure from injection of extracts of the infundibular lobe, after severance of the cord below the medulla, and in one case after removal of most of the thoracic part of the spinal cord in addition, thus indicating that the constriction of the blood vessels is probably a peripheral effect, and not due to

stimulation of the vaso-motor centers. These observations that I present here only incompletely may be taken to indicate that the infundibular lobe of the hypophysis is, in all probability, not a rudimentary organ, but a structure that has some important physiological activity. Moreover, its function is probably different from that of the glandular lobe, and possibly quite independent of it. With regard to the function of the glandular lobe, the method of injecting extracts into the circulation of a normal animal seems to teach us nothing. While the negative results thus obtained do not oppose, they cannot be said to support, the favorite hypothesis that this part of the hypophsis cerebri has a function resembling that of the thyroid lobes. I venture to suggest that this supposed similarity in function might be tested most satisfactorily upon human beings by feeding the gland in cases of myxoedœma or goitre and ascertaining whether a reaction similar to that caused by the thyroid can be obtained.

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*ON THE RELATIVE VARIATION AND CORRELATION IN CIVILIZED AND UNCIVILIZED RACES.**

THE general conclusion would then be that, with increased civilization, absolute size† and variation tend to increase, while correlation, to judge by the males, is stationary; to judge by the females, tends to increase.

It will be found somewhat difficult to reconcile these results with any simple applications of the principle of natural selection. In the first place increased variation undoubtedly suggests a lessening of the struggle for existence, and there can be no question that this increase has gone on among civilized races (See 'Variation in Man and Woman'). The lessening of the struggle has probably been greater for woman than man; hence the principle of natural selection might help to explain the preponderance of variability in civilized woman. The increase in size with civilization seems, on the average, also incontestable. But is it the effect of lessening the struggle for existence? The possibilities may, perhaps, be summed up as follows:

(*a*) The civilized races may have survived owing to their superior size. It may be a result of the struggle in the past. To this must be objected that the increase of size appears to be a progressive change still going on, and yet increase of variation should show a lessening struggle for existence.

(*b*) The effect of suspending natural selection may be to increase size. This would be a blow for panmixia, for we might naturally have expected a regression to the smallness of the more primitive races. It would leave unexplained the apparently smaller progress of women as compared with men, for in their case we might argue from the variation that the struggle for existence is relatively less than in the case of man.

(*c*) The larger size of the civilized races may be due to better food supply and better physical training; in short, it may be due, not to evolution, but to better conditions of growth. This hypothesis does not involve the assumption that acquired characters are inherited. Diminish the food supply and abolish physical training, and the size would sink to the level at which natural selection had left it. Physical

* Conclusion of a communication made to the Royal Society.

† This is only *generally* true, not in every individual case. The French femur is longer than that of the Aino, of neolithic man, and of the ancient inhabitants of the Canary Islands. On the other hand, the French femur appears to be slightly less than the Libyan, although the humerus is somewhat greater. The French women appear in all long bones less than the Libyan women.